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## Effects of perinatal PCB and dioxin exposure and early feeding mode on child development

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## Chapter 3

# Determinants of polychlorinated biphenyl levels in plasma from 42-month-old children

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### ABSTRACT

**Objectives.** We report on the PCB levels in plasma from 42-month-old children, and the factors that determine these levels.

**Methods.** We measured the levels of the PCB congeners 118 (2,4,5-3'4' pentachlorobiphenyl (CB)), 138 (2,3,4-2'4'5'hexaCB), 153 (2,4,5-2'4'5'hexaCB), and 180 (2,3,4,5-2'4'5'heptaCB) in cord plasma, breast milk, and plasma from 42-month-old children (n=126) living in the Groningen area, The Netherlands. The sum of the levels of these four congeners was calculated for cord plasma ( $\Sigma\text{PCB}_{\text{cord}}$ ), breast milk ( $\Sigma\text{PCB}_{\text{milk}}$ ), and 42-month plasma ( $\Sigma\text{PCB}_{42\text{mo}}$ ).  $\Sigma\text{PCB}_{\text{cord}}$  was used as a measure of prenatal exposure. Postnatal exposure was assessed in terms of the  $\Sigma\text{PCB}_{\text{milk}}$  and the duration of lactation. In addition, maternal factors including age, body weight and height, parity, formal education were recorded.

**Results.** In 42-month-old children who have been fully breast-fed for at least six weeks as babies, the median  $\Sigma\text{PCB}_{42\text{mo}}$  was 4½ times as high as that in formula-fed children (0.81  $\mu\text{g/L}$  vs. 0.18  $\mu\text{g/L}$ ). The PCB levels in cord blood and human milk, and the duration of breast-feeding predict the plasma PCB level at 42 months. Each additional week of full breast-feeding is estimated to result in an increase of 0.3% of the milk PCB level.

**Conclusion.** Lactation is a major source for the child's PCB body burden at 42 months.

### INTRODUCTION

Polychlorinated biphenyls (PCBs) are polycyclic aromatic compounds, that are widespread environmental pollutants. In the 'Western world', PCBs were used in a wide range of industrial products, such as fire retardants, paint additives, plasticizers, and dielectrical fluids in capacitors and transformers, until they were banned in the late 1970s. There are 209 possible PCB congeners, which all differ in their chlorine substitution pattern and

their degree of chlorination. They are highly lipophilic, chemically stable, and resistant to breakdown by acids, bases, heat and hydrolysis. Due to these chemical properties, PCBs are difficult for living organisms to excrete. PCBs therefore tend to bioaccumulate in the foodchain. Prolonged exposure to relatively small amounts of PCBs leads to high levels of these compounds in species at the top of the food chain, including fish, birds, wildlife, and human beings. Food is the major source (>90%) of human exposure. In The Netherlands, dairy products are the major contributors to the daily intake of PCBs<sup>1</sup>.

PCBs can be found in all fat compartments of the human body, including blood and adipose tissue<sup>2</sup>. They cross the placenta and are transferred into breast milk, exposing the offspring during fetal life and infancy<sup>3</sup>. Breast milk contains relatively large quantities of these compounds, and in the baby almost complete absorption takes place<sup>4, 5</sup>. In infant formula milks, no detectable amounts of PCBs have been found. The latter is due to the fact that, in the process of infant formula production, cow's milk lipids are replaced by fats of vegetable origin.

In the present study, we report on the PCB levels in plasma obtained from 42-month-old toddlers that have been breast- or formula-fed as babies, and the factors that determine these levels.

#### SUBJECTS AND METHODS

From June 1990 until 1992, healthy pregnant women were asked to participate in the study. The planned sample size was 100 breast-feeding and 100 formula-feeding mothers. Eligible women were approached by their midwives or obstetricians between the 32nd and 34th week of pregnancy. To be eligible, women had to be healthy (i.e. not suffering from a serious illness); had to live in Groningen or surroundings, which is a semi-industrialized region in the Northeastern part of the Netherlands; had to be of caucasian origin; had to have no history of direct exposure to PCBs; and had to have no more than one other child. The current child had to be healthy and born at term. The mothers were provisionally assigned to one of the two feeding groups on the basis of their intention to breast- or formula-feed their infant. In the breast-feeding group, we only included mothers who were able to sustain full breast-feeding for at least six weeks. In the formula-feeding group, formula milk from a single batch (Almiron M2; Nutricia N.V.; The Netherlands) was provided. In the latter group, children were exclusively fed on formula-milk during the first six months after birth. For each mother, the age at delivery, the parity, and the

formal education was recorded. In addition, the maternal pre-pregnancy body weight and height were noted and used to calculate the body mass index (BMI; weight (kg)/height (m)<sup>2</sup>). The BMI is an indicator of fat stores. Also, data on the number of weeks of full and partial breast-feeding was collected. The medical ethics committee of the University Hospital Groningen approved the protocol.

Immediately after birth, blood was obtained from the umbilical cord. When the children were 42 months of age, a 5 ml blood sample was taken by means of venipuncture. Parental consent was obtained. Plasma and cells were separated by centrifugation at 3,000 rpm for ten minutes. The plasma samples were stored at minus 20°C until PCB analysis. From the breast-feeding mothers, milk was collected as a 24-hour sample in the second week after delivery by emptying both breasts with an electrical pump (Babyluxus 2, KAWECO, Stuttgart, Germany). 10% aliquots were pooled and stored at -20°C. The remaining breast milk was given to the infant by bottle. The PCB congeners nr. 118 (2,4,5-3'4' pentachlorobiphenyl (CB)), 138 (2,3,4-2'4'5' hexaCB), 153 (2,4,5-2'4'5' hexaCB), and 180 (2,3,4,5-2'4'5' heptaCB) were determined in plasma and breast milk by means of gas chromatography with electron capture detection<sup>6, 7</sup>. The same measurements were done in samples of the formula milk. All PCB measurements were performed at the TNO-nutrition laboratories in Zeist, The Netherlands. The levels of these four congeners are relatively high, and therefore measurable at reasonable levels of accuracy and precision. The sum of the levels of these four congeners was calculated for cord plasma ( $\Sigma\text{PCB}_{\text{cord}}$ ), breast milk ( $\Sigma\text{PCB}_{\text{milk}}$ ), and plasma obtained from the 42-month-olds ( $\Sigma\text{PCB}_{42\text{mo}}$ ). The  $\Sigma\text{PCB}_{\text{cord}}$  was used as a measure of prenatal exposure. Postnatal exposure to PCBs from nursing was assessed in terms of the  $\Sigma\text{PCB}_{\text{milk}}$  and the number of weeks during which full ( $\Sigma\text{PCB}_{\text{milk}} \times \text{duration of full nursing}$ ) and partial ( $\Sigma\text{PCB}_{\text{milk}} \times \text{duration of partial nursing}$ ) breast-feeding had been given. A more detailed description of the sampling and analytical methods can be found in a previous report<sup>8</sup>.

The chi-square, the Student's t-test, and the Mann-Whitney U test were used to compare groups. The  $\Sigma\text{PCB}_{\text{milk}}$ , the  $\Sigma\text{PCB}_{\text{cord}}$ , and the  $\Sigma\text{PCB}_{42\text{mo}}$  were logarithmically transformed. The effect of prenatal and lactational exposure on the plasma PCB levels at 42 months was evaluated by multiple regression analysis. The  $\Sigma\text{PCB}_{42\text{mo}}$  was the dependent variable. The maternal age, the body weight and height at delivery, the BMI, the parity, and the formal education of the mother, the initial mode of feeding, the  $\Sigma\text{PCB}_{\text{cord}}$ , and the PCB exposure during full nursing were the independent variables. A p-value of 0.05 or less was considered significant.

## RESULTS

Two hundred and eleven mothers and their children took part in this study. 104 (49%) of these women were in the breast-feeding group, and 107 (51%) belonged to the formula-feeding group. In the perinatal period, 191 cord plasma samples and 99 breast milk samples were collected. At the age of 42 months, blood was sampled from 126 (60%) children, and analyzed for PCBs. The main reason for not obtaining a plasma sample from the 85 remaining toddlers was the inability of the parents to visit the hospital due to practical problems, such as the pregnancy of the mother, or the absence of care for siblings. The children whose blood was sampled at 42 months of age did not significantly differ from those whose blood could not be obtained at this age in terms of feeding mode, duration of full breast-feeding, cord plasma and breast milk PCB levels (table 1). Table 2 presents the characteristics of the final study group.

At birth, the median  $\Sigma\text{PCB}_{\text{cord}}$  was significantly ( $p < 0.01$ ) higher in the breast-fed group ( $0.39 \mu\text{g/L}$ , range:  $0.17\text{--}1.1$ ;  $n=58$ ) as compared to that in the formula-fed group ( $0.32 \mu\text{g/L}$ , range:  $0.12\text{--}0.83$ ;  $n=57$ ). At 42 months, in the breast-fed group, the median  $\Sigma\text{PCB}_{42\text{mo}}$  was equal to  $0.81 \mu\text{g/L}$  (range:  $0.23\text{--}2.2 \mu\text{g/L}$ ), whereas it was  $0.18 \mu\text{g/L}$  (range:  $0.07\text{--}1.49$ ) in the formula-fed children ( $p < 0.001$ ). The median  $\Sigma\text{PCB}_{\text{milk}}$  was  $11.9 \mu\text{g/L}$  (range:  $3.3\text{--}28.2 \mu\text{g/L}$ ;  $n=58$ ). In the formula milk samples, the levels of the PCB congeners nr. 118, 138, 153, and 180 were found to be below the limit of detection. Figure 1 shows the congeneric pattern of the mother's milk. Figure 2 presents the median levels of the individual PCB congeners (i.e. congeners nr. 118, 138, 153, and 180) at birth and at 42 months of age for, respectively, the breast- and the formula-fed children.

The regression analysis resulted in the following model:

$$\Sigma\text{PCB}_{42\text{mo}} = 0.429 (SE=.149) * 0.820 (SE=.281)^{FM} * \Sigma\text{PCB}_{\text{cord}}^{0.544 (SE=.136)} + 0.0028 (SE=.00055) * \text{FBF} * \Sigma\text{PCB}_{\text{milk}},$$

where FBF stands for the number of weeks of full breast-feeding, which incase of bottle-feeding is equal to 0. FM, which stands for feeding mode, takes the value 0 for breast-fed children and 1 for bottle-fed children. This non-linear model explains 75% of variance. Each week of additional breast-feeding is estimated to increase the  $\Sigma\text{PCB}_{42\text{mo}}$  by 0.28% ( $SE=0.05\%$ ) of the  $\Sigma\text{PCB}_{\text{milk}}$ . For a mother with a median  $\Sigma\text{PCB}_{\text{milk}}$  (i.e.  $11.9 \mu\text{g/L}$ ) this amounts to an increase of  $0.033 \mu\text{g/L}$  per week of full breast-feeding. The maternal factors, including the age, the pre-pregnancy body weight and height, the BMI, the parity, the formal education, and the

child's exposure to PCBs during partial breast-feeding were not significantly associated with the  $\Sigma\text{PCB}_{42\text{mo}}$ , and were dropped from the model.

**Table 1:** Characteristics\* of the participants and the non-participants in the final study population.

Variables	Participants		Non-participants	
	n	outcome	n	outcome
Feeding mode				
% Breast-fed	126	50	85	48
Duration of full breast-feeding				
median (range; wks)	63	14 (6-30)	41	14 (6-30)
$\Sigma\text{PCB}_{\text{cord}}^{\dagger}$				
median (range; $\mu\text{g/L}$ )	115	0.35 (0.12-1.10)	76	0.37 (0.08-0.81)
$\Sigma\text{PCB}_{\text{milk}}^{\ddagger}$				
median (range; $\mu\text{g/L}$ )	58	11.9 (3.3-28.2)	37	10.9 (5.8-31.0)

\* data concern 211 mother/infant pairs. Differences between groups are not significant,  $\dagger \Sigma\text{PCB}_{\text{cord}}$  sum of the levels ( $\mu\text{g/L}$ ) of the PCB congeners 118, 138, 153, and 180 in cord plasma,  $\ddagger \Sigma\text{PCB}_{\text{milk}}$  sum of the levels ( $\mu\text{g/L}$ ) of the PCB congeners 118, 138, 153, and 180 in breast milk.

## DISCUSSION

Lactation is a major source for the PCB body burden in 42-month-old children. The median 42-month plasma PCB level of children that have been breast-fed for at least six weeks was 4½ times as high as that of formula-fed children. Each additional week of full breast-feeding was estimated to result in an increase of about 0.3% of the milk PCB level. Our study population consisted of 126 mother/child pairs which can be considered typical for The Netherlands<sup>9</sup>. PCB levels in plasma and breast milk in The Netherlands are comparable to those found in other parts of the industrialized Western world, including the United States of America<sup>10-13</sup>. It should be mentioned that the effect of the intake by the children of

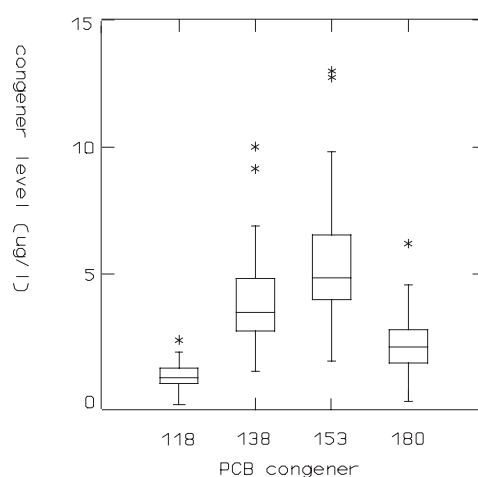
**Table 2:** Baseline characteristics of the study group.

Variables	Breast-fed	Formula-fed
Number of children	63	63
Sex		
% boys	48	51
Birth weight		
mean $\pm$ SD (g)	3624 $\pm$ 510	3477 $\pm$ 412
Maternal pre-pregnancy weight		
mean $\pm$ SD (kg)	66 $\pm$ 9	68 $\pm$ 11*
Maternal height		
mean $\pm$ SD (cm)	171 $\pm$ 6.5	171 $\pm$ 6.0
Maternal BMI†		
median (range)	22 (16 - 32)	22 (17 - 32)
Maternal age at delivery		
mean $\pm$ SD (years)	31 $\pm$ 3	28 $\pm$ 4*
Duration of full breast-feeding		
median (range; weeks)	14 (6 - 30)	0
Duration of partial breast-feeding‡		
median (range; weeks)	3 (0 - 52)	0
Formal education of the mother		
% higher education§	76	15*

\* significantly different from the breast-feeding group ( $p < 0.05$ ), † BMI body mass index [weight (kg)/height (m)<sup>2</sup>], ‡ number of weeks during which the child was fed on both breast and formula milk, § professional or university training.

food products other than breast- or formula milk on 42-month PCB levels was not determined, as we have no information on this matter.

Among the infants of mothers who decided to breast-feed, the median PCB level in cord plasma was significantly higher than that among children whose mothers preferred formula-feeding. This difference in cord plasma levels can be attributed to differences in the mother's dietary intake of PCBs, and the mean maternal age (see: [table 2](#)). In the Dutch setting, formula-feeding mothers have been found to consume less dairy



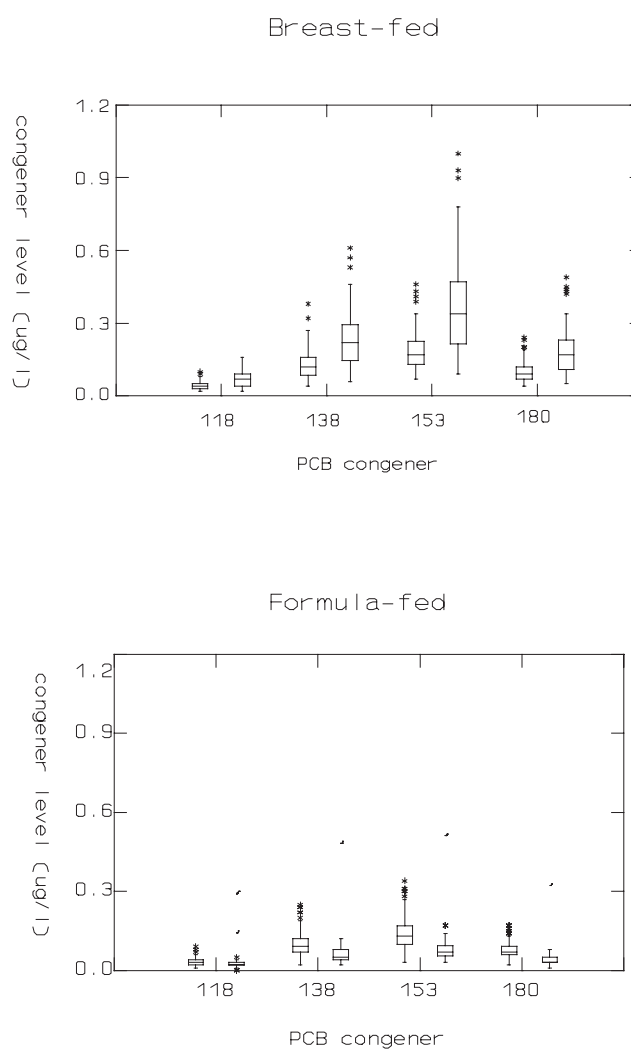
**Figure 1:** Levels of the PCB congeners nr. 118, 138, 153, and 180 in breast milk (n=63).

products and beef, which are relatively high in PCBs, as compared to their breast-feeding counterparts<sup>1</sup>. Furthermore, women who decided to bottle-feed their infant were younger at the time of delivery. This implies that formula-feeding mothers have been subjected to a shorter period of PCB intake than the breast-feeding women.

Contrary to prenatal exposure<sup>8-12</sup>, adverse effects of postnatal PCB exposure have seldomly been found. One study showed a negative relationship between blood PCB levels at four years of age and behavioral activity level<sup>13</sup>. This behavioral effect of postnatal PCB exposure was found to be subtle, and its clinical relevance is uncertain. Today the influence of perinatal PCB exposure on human sexual development and fertility is a major issue in PCB research. As yet the impact of PCB exposure on these aspects is unclear<sup>15</sup>.

In conclusion, the plasma PCB level at pre-school age are related to the duration of full breast-feeding, and the PCB levels in cord plasma and human milk.





**Figure 2:** Levels of the PCB congeners nos. 118, 138, 153, and 180 in plasma from breast- ( $n=63$ ) and formula-fed ( $n=63$ ) children. For each congener, the left box plot gives the levels at birth and the right plot gives the levels at 42 months of age.

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